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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 311/58, C07B 53/00, 55/00

A1

(11) International Publication Number: **WO 99/59988**

(43) International Publication Date: 25 November 1999 (25.11.99)

(21) International Application Number: PCT/SE99/00767

(22) International Filing Date: 6 May 1999 (06.05.99)

(30) Priority Data:
9801726-2 15 May 1998 (15.05.98) SE

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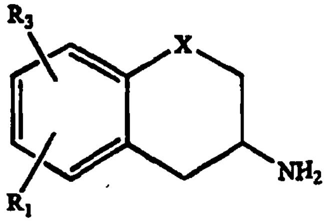
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NEW PROCESS

(57) Abstract

A process for the preparation of one of the enantiomers of an amine of formula (I) which comprises resolution of a racemate of the corresponding carboxylic acid and Curtius rearrangement of the desired enantiomer from said resolution, the other enantiomer from said resolution being subjected to a racemization for conversion to said desired enantiomer and recirculation of the latter to said resolution and Curtius rearrangement operations.



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NEW PROCESS

Technical field

The present invention is within the field of stereospecific compounds. More specifically, it relates to a new process for the preparation of one of the enantiomers of a group of amines, said enantiomer being obtained in a high yield and in a highly purified state. The invention also relates to some of those partial steps which are utilized in said process.

Background of the invention

WO93/07135 discloses the (R)-enantiomer of 3-(N-isopropyl-N-n-propylamino)-5-(5-isopropyl)carbamoyl-chroman as an especially interesting therapeutically active compound, e.g. for use in the treatment of 5-hydroxytryptamine mediated states and disorders. In one of the methods disclosed therein for the preparation of 3-amino-5 methoxy-chroman is enantiomerically separated into the (R)- and (S)-enantiomers thereof. Said (R)-enantiomer is then used as an intermediate in the preparation disclosed therein.

Other therapeutically active chroman or benzopyran compounds are disclosed in WO91/09853 and EP 222 996, and one of the enantiomers of the corresponding aminochromans may be useful as an intermediate in the preparation thereof in those cases where the corresponding enantiomers of said chroman compounds are of specific interest.

The present invention provides a new process for the preparation of one of the enantiomers of chroman/(3,4-dihydro-2H-benzopyran)-amine as well as of tetraline amines. Such enantiomers can for instance be used as intermediates in the preparations of the above-mentioned therapeutically active chroman compounds and therapeutically active tetraline compounds. However, the invention is not restricted in any respect as concerns the use of the end product of the process claimed, as said end product can of course be used as an intermediate in any applicable process or even as a valuable end product *per se*. Nor is the invention restricted to the preparation of the (R)-enantiomer. Thus, in other cases the (S)-enantiomer may be the most valuable one, and the invention is applicable also to the preparation thereof. Therefore, for convenience, the terms ″desired″ enantiomer and ″non-desired″ or ″other″ enantiomer will be used hereinafter.

General disclosure of the invention

In accordance with the present invention it has unexpectedly turned out that several advantages can be achieved if performing a resolution at an earlier stage in the reaction sequence to the (R)-enantiomer of the desired amine than the resolution disclosed in WO93/07135, i.e. the resolution of the racemic mixture of 3-amino-5-methoxychroman.

More specifically the present invention is based on a resolution of a racemic mixture of the corresponding carboxylic acid rather than of the amine, the desired enantiomer obtained by said carboxylic acid resolution then being converted to the same enantiomer of the corresponding amine by a Curtius rearrangement.

Thus, firstly the Curtius rearrangement from the desired enantiomer of the carboxylic acid to the desired enantiomer of the amine has been found to be highly stereospecific, i.e. a very minor or no racemization takes place therein.

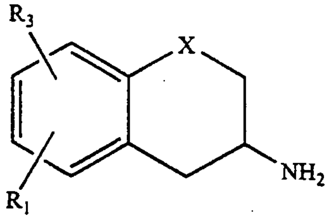
Secondly, contrary to the prior art process where the desired enantiomer of the amine is the only useful product, also the other enantiomer can be utilized in the process according to the present invention. More specifically, while it has not been possible to accomplish a racemization of the previously known (S)-amine, which in practice means a loss of at least 50% of the raw material used, the present invention involves a racemization of the(S)-carboxylic acid. The racemate thereby obtained can then be subjected to a new resolution to the formation of more of the desired (R)-isomer.

In other words the process claimed is also extremely advantageous from an economical and material utilization point of view.

Furthermore, outstanding yields and purities have been obtained by the new process.

Detailed description of the invention.

According to a first aspect of the invention a process is provided for the preparation of one of the enantiomers of an amine of the formula (I):

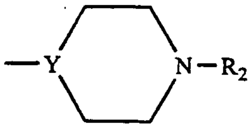


(I)

wherein

X is O or CH_2;

R_1 is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, halogen, OH, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6 alkyl, or



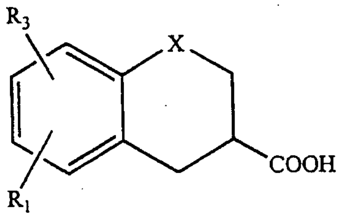
where Y is N or CH; and

R_2 is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl or benzyl; and

R_3 is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, halogen, OH, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6 alkyl, OCF_3, $OCHF_2$, OCH_2F, CN, NO_2, CF_3, SO_3CH_3, SO_3CF_3, NR_4R_5 or $SO_2NR_4R_5$, where R_4 is H,

C_1-C_6-alkyl or C_3-C_6-cycloalkyl and R_5 is H, C_1-C_6-alkyl or C_3-C_6-cycloalkyl;
in the form of the free base or a salt or hydrate thereof, which salt or hydrate is preferably pharmaceutically acceptable, which comprises the following steps:

a) subjecting a racemic mixture of a carboxylic acid of the formula (II):



(II)

or a base addition salt or solvate thereof, wherein X, R_1 and R_3 are each as defined in connection with formula (I), to a resolution operation so as to obtain the desired enantiomer and the other enantiomer of said carboxylic acid of formula (II);

b) separating said desired enantiomer from said other enantiomer;

c) subjecting said other enantiomer from step b) to a racemization operation so as to convert the same into a racemate of said carboxylic acid of formula (II);

d) optionally isolating said racemate obtained in step c) in a purified state;

e) recycling and subjecting the racemate as obtained in step c), or alternatively in step d), to a resolution operation as defined in step a) and separating the desired enantiomer thereof as defined in step b);

f) optionally repeating the operations defined in steps c)-e) one or more times;

g) subjecting said desired enantiomer of the carboxylic acid (II) as separated in step b) to a Curtius rearrangement to convert the same into said desired enantiomer of the amine of formula (I);

h) optionally subjecting said desired enantiomer of the amine of formula (I) as obtained in step g) to a resolution operation, the desired enantiomer thereby obtained being recovered; and

i) optionally making base, salt and/or hydrate conversions and/or R_1 and/or R_3 conversions, as appropriate, at any stage(s) of the process.

Thus, the starting material of the new process according to the present invention is a racemic mixture of a carboxylic acid of formula (II). Such a carboxylic acid can easily be prepared by known methods. In this context reference could be made for instance to Acta Pharm.Suec. 24, 169-182, (1987), which specifically discloses 5-methoxy-2H-chroman-3-carboxylic acid. As concerns the term ”racemic mixture”, it should of course be interpreted in a broad sense. That is, in principle a mixture of the two enantiomers in any proportions should be useful in connection with the invention. However, generally a common 50:50 mixture of said enantiomers is used.

As can be gathered by a person skilled in the art said starting material need not be the acid per se but may also be a base addition salt or solvate thereof. Said base addition salt may be derived form any inorganic or organic base in accordance with prior art. Examples of suitable inorganic base salts are, however, sodium, potassium, lithium, ammonium, calcium and magnesium salts. In connection with organic base salts isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine salts could especially be referred to.

In step a) said starting material is subjected to a resolution operation which can be performed by resolution techniques previously known per se. Generally, however, this means a reaction between the starting acid and an optically active base, preferably an optically active amine, a salt of the desired enantiomer thereby being formed.

A preferable group of useful amines is arylalkylamines, the aryl unit thereof e.g. being phenyl and the alkyl unit e.g. being C_1-C_6-alkyl (preferably methyl, ethyl or butyl). A specific example thereof is phenylethylamine, such as (R)-(+)- or (S)-(-)-1-phenylethylamine.

As mentioned, said resolution is accomplished according to known principles. Preferably, however, such conditions are used by which the enantiomeric salt is caused to crystallize. Thereby the separation of said salt from the reaction mixture will be facilitated. The crystal salt form should also make a purification thereof easier, for instance by means of a recrystallization. Such a crystallization is advantageously performed from a suitable polar or semi-polar solvent or combinations of such solvents, e.g. H_2O, acetone, isopropyl acetate, isopropanol, ethanol, H_2O/ethanol, H_2O/acetone and isopropyl acetate/isopropanol.

In step b) the desired enantiomer obtained from step a) is separated from the other enantiomer according to any known separation technique. In case of a crystallization of the desired enantiomer in step a) said separation is preferably performed as a filtration thereof.

The other enantiomer from step b) is then subjected, in step c), to a racemization to the formation of a racemate of said carboxylic acid of formula II. Before said racemization, however, it is preferably subjected to a work-up procedure, primarily to remove excess of the optically active base used in step a)and to reconvert the salt into the free acid before the racemization is conducted.

The racemization in step c) can be conducted in accordance with principles known per se for the racemization of optically active carboxylic acids. One available method is for instance disclosed in Ruechardt, Gartner and Salz, Chem.Int. Ed. Eng., 23, 162 (1984), which method is based on the use of acetic anhydride and pyridine. However, in connection with the present invention it has been found especially preferable to utilize a technique generally disclosed in US Patent No. 4,946,997, the disclosure of which is hereby incorporated by reference.

More specifically, it has been found that when treating the other enantiomer of the fused ring (chroman or tetraline) carboxylic acid referred to with an acid anhydride and a conjugate base thereof, an extensive racemization of said enantiomer takes place. Similar results have also been obtained with a combination of acid anhydride and a tertiary amine.

Preferably an organic acid anhydride and a conjugate base thereof is utilized, but in general any acid anhydride and its corresponding conjugate base may be employed provided they do not react with other functional groups in the molecule. Said proviso is of course applicable to any one of the stages used in the process of the present invention, i.e. that considerations have to be made to avoid secondary reactions in accordance with known principles. A specific example of a useful acid anhydride/conjugate base combination is acetic anhydride/sodium acetate. Although the sodium base is the preferred one, other alkali metal or rare earth metal bases may also be employed. An organic acid anhydride, e.g. acetic anhydride is especially interesting also in the case of a tertiary amine. One example of a useful tertiary amine is triethylamine.

The racemization is generally performed in a solvent, preferably an organic solvent, and preferably at the reflux temperature thereof. Especially, a polar solvent is used, such as isopropyl acetate and/or tetrahydrofuran, isopropyl acetate being most preferred. Examples of other useful solvents are ethyl acetate, dioxane and toluene (semipolar). Generally, the racemization is conducted at the reflux temperature of the solvent used.

The amount of acid anhydride/conjugate base generally is in the range of 5-50 mol-%, or even more, of that of said other enantiomer, preferably 5-20 and especially around 10 mol-%.

Before recycling (in step e)) the racemate obtained in step c) to a resolution operation as defined in step a), it is optionally isolated in a purified state. Said isolation can e.g. be accomplished by means of a crystallization operation, the crystals obtained thereby being isolated in any conventional way, e.g. by filtration.

The racemate is then recycled and subjected to said resolution operation performed similar to that of step a). As to the conditions to be used therein reference is thus made to the description of step a).

Although the process claimed may be performed in a continuous or semi-continuous manner a batchwise process is generally utilized and here said recycling in step e) is made on a resolution batch subsequent to that resolution operation batch from which said racemate originates. Preferably the recycling is made on the batch next to that from which said racemate originates.

According to an especially preferable embodiment of the invention said recycled racemate is combined with a new feed of racemic mixture of carboxylic acid of formula (II) such that the total amount of racemic mixture fed to said subsequent step a) is essentially the same as the amount of racemic mixture fed to original step a). Hereby, the same equipment and batches of substantially similar sizes (volume) can be used in batchwise processes in spite of the recycling(s) made in accordance with the invention.

The desired enantiomer from said new resolution is then separated from the other enantiomer as previously defined in step b). Said other enantiomer is preferably subjected to further operations similar to those defined in steps c)-e) for further recovery of "desired" enantiomer from "non-desired" enantiomer. Such further operations can be repeated one, two, three or four times, or even more, optimum results being easily established by a person skilled in the art in each specific case

The enantiomer separated in step b), i.e. the desired enantiomer from the first step a) plus one or more further steps a), is thereafter, in step g), subjected to a Curtius rearrangement to convert the same into the corresponding enantiomer of the amine of formula I. As mentioned above, such a Curtius rearrangement has turned out to be very stereospecific.

General principles for Curtius rearrangements can be used, as is disclosed in literature concerning this technical field.

If desired, the product as obtained from step g) can be purified even further, for instance by means of a resolution operation. Said resolution can be conducted in a manner known per se, preferably by a base-acid reaction while using an optically active acid. Examples of useful acids are mandelic acid, camphorsulfonic acid, glucuronic acid, tartaric acid and derivatives thereof, where e.g. (L)-(+)- or (D)-(-)-tartaric acid has been found to give a very high yield and purity. Also derivatized chiral acids may be used for said resolution. Any suitable polar or semi-polar solvent or combination thereof (see the resolution of step a)) can be used in this respect, e.g. H_2O, methanol and ethanol.

The desired enantiomer is then recovered in any suitable way and form, depending on the intended use thereof. This may for instance involve common base, salt and/or hydrate conversions, which conversions need not necessarily be made after the above-mentioned Curtius rearrangement but could be made at any stage of the total process. Furthermore, R_1 and/or R_3-substituent insertions, removals or interconversions are within the scope of the invention while considering known principles for reactions interfering with the reactions desired by the invention (use of protective groups, if necessary, etc.). Also said R_1 and/or R_3 reactions can be performed at any stage of the process.

Although the invention has been presented above while specifically referring to compounds wherein R_1 is methoxy and R_3 is hydrogen, it is generally applicable to compounds wherein R_1 and R_3 have the meanings defined above. In connection with these meanings the terms used should be interpreted as follows.

C_1-C_6-alkyl can be straight or branched and includes methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, neo-pentyl, n-hexyl and i-hexyl.

C_1-C_6-alkoxy can be straight or branched and includes methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, i-pentyloxy, t-pentyloxy, neo-pentyloxy, n-hexyloxy and i-hexyloxy.

C_3-C_6-cycloalkyl may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably cyclohexyl.

The meanings referred to above concerning C_1-C_6-alkyl and C_1-C_6-alkoxy are applicable also to said units in the term C_1-C_6-alkoxy-C_1-C_6-alkyl.

Halogen may be fluoro, chloro, bromo or iodo.

The positions of substituents R_1 and R_3 can be any position of the aromatic ring. Especially preferable embodiments, however, are represented by positions 5 and 8 of the ring system of the starting and/or end compound. That is, R_1 may be in position 5 and R_3 in position 8 or vice versa. When X is O, R_1 is more preferably in position 5, and when X is CH_2, R_1 is more preferably in position 8.

Both organic and inorganic acids can be used to form acid addition salts of the amines prepared by the process according to the invention. Preferably such acids are non-toxic and pharmaceutically acceptable although this is not always necessary, especially when the amines referred to are to be used as intermediates only, Illustrative acids are sulfuric, nitric, phosphoric, oxalic, hydrochloric, formic, hydrobromic, citric, acetic, lactic, tartaric, dibenzoyltartaric, diacetyltartaric, palmoic, ethanedisulfonic, sulfamic, succinic, propionic, glycolic, malic, gluconic, pyruvic, phenylacetic, 4-aminobenzoic, anthranilic, salicylic, 4-aminosalicylic, 4-hydroxybenzoic, 3,4-dihydroxybenzoic, 3,5-dihydrobenzoic, 3-hydroxy-3-naphthoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethansulfonic, benzenesulfonic, p-toluenesulfonic,sulfanilic, naphthalenesulfonic, ascorbic, cyclohexylsulfamic, fumaric, maleic and benzoic acids. These salts are readily prepared by methods known in the art.

According to another aspect the invention also relates to that partial step of the total process disclosed above where one of the enantiomers of a carboxylic acid of formula (II) above, or a salt of hydrate thereof, is prepared from a racemic mixture or the corresponding acid by means of a resolution of said racemic mixture as defined in step a) above followed by steps c) and e) and optionally d), f) and i) as also defined above.

Thus, as mentioned said resolutions and racemizations have been found to give interesting results when performed on the fused ring compounds referred to.

Steps a), c)-f) and i) in connection with this aspect of the invention can be conducted as the corresponding steps in connection with the first process of the invention and need not be repeated here.

A still further aspect of the invention is represented by a process for the preparation of one of the enantiomers of an amine of formula (I), as defined above, or a salt or solvate thereof, which comprises subjecting the corresponding enantiomer of a carboxylic acid of formula (II), as defined above, or a salt or solvate thereof, to a Curtius rearrangement as defined in step g) of the first process of the invention, and then optionally performing steps h) and i) of said first process. Thus, as mentioned above, outstanding results have been obtained when performing such a Curtius rearrangement on the chroman or tetraline compounds referred to.

Details concerning said steps g) h) and i) can be taken from the disclosure of the first process of the invention and need not be repeated here.

EXAMPLES

The invention will now be further illustrated by the following non-limiting working examples.

EXAMPLE 1

(R)-(+)-1-Phenylethylammonium-(R)-5-methoxy-2H-chroman-3-carboxylate

5-Methoxy-2H-chroman-3-carboxylic acid (50.2 g, 241 mmol, 1.0 eq.) and isopropyl acetate (400 ml) were charged to a 1000 ml three necked round bottomed flask fitted with a mechanical stirrer. The mixture was heated at about 82°C to a clear solution and a solution of (R)-(+)-phenylethylamine (29.2 g, 241 mmol, 1.0 eq.) in isopropyl acetate (100 ml) was added. The solution was slowly cooled to about 10°C (~ 1h), where the formed crystals of the title compound were separated by filtration and washed with cold isopropyl acetate (2x25 ml).

Yield:	Theoretical:	39.7 g
	Found:	39.1 g (98%)

Enantiomeric purity: 96.8 : 3.2 (R/S)

EXAMPLE 2

(S)-5-Methoxy-2H-chroman-3-carboxylic acid

The mother liquid from Ex. 1 (~ 550 ml) and H_2O (100 ml) were added to a 1000 ml three necked round bottomed flask fitted with a mechanical stirrer. The solution was acidified (pH=1.2) with conc. HCl (11 ml) and then stirred for about 10 minutes before being transferred into a separation funnel. The H_2O phase was separated and the organic phase was washed with acidic (pH = 1.2) H_2O (100 ml) for about 10 minutes. The organic phase containing the title compound was then dried with Na_2SO_4 and evaporated to dryness.

Yield:	Theoretical:	25.1 g
	Found:	23.8 g (95%)

Enantiomeric purity: 13.6 : 86.4 (R/S)

EXAMPLE 3

(R,S)-5-Methoxy-2H-chroman-3-carboxylic acid

(S)- 5-Methoxy-2H-chroman-3-carboxylic acid from Ex. 2 (23.8 g, 112 mmol), dry isopropyl acetate (250 ml), sodium acetate (1.92 g, 23.2 mmol, 20 mole-%) and acetic anhydride (1.32 g, 23..5 mmol, 20 mole-%) were charged to a dry 500 ml three necked round bottomed flask fitted with a mechanical stirrer. The reaction mixture was heated to reflux (about 82°C) for 16 h. H_2O (25 ml) was added while the solution was still hot, said solution then being cooled to 30-40°C, when conc. HCl (3 ml) was added dropwise to pH<1.0. The solution was stirred at 20°C and then transferred to a separation funnel. The H_2O phase was separated and the organic phase was washed with acidic (pH<1.0) H_2O (25 ml) for about 10 minutes. The organic phase containing the title compound racemate was dried with Na_2SO_4 and evaporated to dryness.

Yield:	Theoretical:	23.8 g
	Found:	22.9 g (96%)

Enantiomeric purity: 49.7 : 50.3 (R/S)

EXAMPLE 4

(R,S)-5-Methoxy-2H-chroman-3-carboxylic acid

To the carboxylic acid from Example 3 was added hot (80°C) isopropyl acetate (48 mL). The mixture was cooled, and at 70°C seed crystals were added. The temperature was lowered to -5°C to initiate crystallization.

Yield: Theoretical: 25.0 g
Found: 18.8 g (75%)
Enantiomeric purity: 49.3 : 50.7 (R/S)

EXAMPLE 5

(R)-(+)-1-Phenylethylammonium-(R)-5-methoxy-2H-chroman-3-carboxylate

The product from Ex. 3, i.e. (R,S)- 5-methoxy-2H-chroman-3-carboxylic acid (22.9 g, 110 mmol) was charged to a 500 ml flask and a resolution was performed as in Ex. 1, giving the title compound.

Yield: Theoretical: 18.1 g
Found: 14.6 g (80.6%)

Enantiomeric purity: 99.4 : 0.6 (R/S)

EXAMPLE 6

(S)-5-Methoxy-2H-chroman-3-carboxylic acid

The mother liquid from Ex. 5 (~300 ml) was transferred to a 500 ml flask and work-up was conducted as in Ex. 2.

Yield: Theoretical: 11.5 g
Found: 12.5 g (104%)

Enantiomeric purity: 8 : 92 (R/S)

EXAMPLE 7

(R,S)-5-Methoxy-2H-chroman-3-carboxylic acid

Said (S)-5-Methoxy-2H-chroman-3-carboxylic acid from Ex. 6 (12 g, 57.6 mmol) was charged to a 250 ml flask and a racemization as in Ex. 3 above was performed, the title compound racemate being obtained.

Yield Theoretical: 12 g
Found: 11.7 g (97.5%)

Enantiomeric purity: 45 : 55 (R/S)

EXAMPLE 8

(R)-(+)-1-Phenylethylammonium-(R)-5-methoxy-2H-chroman-3-carboxylate

The product from Ex. 7, i.e. (R,S)-5-methoxy-2H-chroman-3-carboxylic acid (11.7 g, 56 mmol) was charged to a 250 ml flask and again a resolution was accomplished as in Examples 1 and 5.

Yield:	Theoretical:	9.2 g
	Found:	7.2 g (78.3%)

Enantiomeric purity: 98.5 : 1.5 (R/S)

EXAMPLE 9

(S)-5-Methoxy-2H-chroman-3-carboxylic acid

The mother liquid from Ex. 8 (~150 ml) was transferred to a 250 ml flask and work-up was conducted as in Examples 2 and 6.

Yield:	Theoretical:	5.8 g
	Found:	6.9g (118%)

Enantiomeric purity: 8.2 : 91.8 (R/S)

EXAMPLE 10

(R)-5-methoxy-2H-chroman-3-carboxylic acid

(R)-(+)-1-Phenylethylammonium-(R)-5-methoxy-2H-chroman-3-carboxylate from Ex. 1 (15.8, 31 mmol) and toluene (90 ml) were charged to a 250 ml three necked round bottomed flask fitted with a mechanical stirrer. The solution was heated to about 80°C and water (40 ml) was added. The mixture was cooled to 30-40°C when conc. HCl (3 ml) was added (pH<1.0). The solution was stirred at room temperature and then transferred to a separation funnel. The H_2O phase was separated and the organic phase was again washed with acidic H_2O (40 ml). The organic phase was finally dried by azeotropic distillation giving the title compound.

Yield:	Theoretical:	10.0 g
	Found:	The product was not isolated

Enantiomeric purity: 98.7 : 1.3 (R/S)

EXAMPLE 11

(R)-3-Amino-5-methoxy-2H-chroman

To a 250 ml three necked round bottomed flask fitted with a mechanical stirrer (R)-5-methoxy-2H-chroman-3-carboxylic acid (18.5 g, 89 mmol, 1.0 eq.)from Example 10, thionyl chloride (11.7 g, 97.8 mmol, 1.1 eq.) and toluene (130 ml) were charged. The solution was heated to about 90°C (gas evolution) for about 3h. Then the solution was cooled to room temperature and QBr (200 mg, 0.9 mol-%) was added. A solution of H_2O (20 ml) and sodium azide (7.0 g, 106.8 mmol, 1.2 eq.) was then dropwise added to the reaction solution, the temperature rising about 10°C during the reaction. When again at room temperature the solution was transferred to a separation funnel and the H_2O phase was separated therefrom. The organic phase was then transferred to a funnel and was dropwise added to a 250 ml flask containing methanol (50 ml), which had been pre-heated to about 60°C. Foaming and gas evolution took place during the reaction. The solution was refluxed and after 2h the reaction was completed. The solution was evaporated to dryness and an oil was obtained. Said oil was dissolved in methanol (35 ml) and transferred to a 250 ml flask. 40% KOH (40 ml) was added in portions and the solution was heated to reflux (60-65°C) for about 18h. The solution was cooled to room temperature and toluene (140 ml) was added. The solution was stirred for about 10 minutes and then transferred to a separation funnel. The H_2O phase was separated therefrom and the organic phase was washed with H_2O (100 ml) for about 10 minutes. The toluene phase was then evaporated to dryness and an oil was obtained. Said oil was redissolved in toluene (175 ml) and H_2O (175 ml) was added. The solution was acidified (pH≅1.0) with conc. HCl (10 ml) and then extracted (about 10 minutes) before being transferred to a separation funnel. The toluene phase was again extracted with acidic H_2O (175 ml) and then discarded. To the H_2O phase toluene (350 ml) was added and the phases were made basic with 45% NaOH (≅15 ml) to pH>11.0. The phases were again transferred to a separation funnel and the H_2O phase was separated therefrom. The toluene phase was dried with Na_2SO_4 and evaporated to dryness to give the title compound as an yellowish oil.

Yield:	Theoretical:	15.9 g
	Found:	11.3 g (71%)

Enantiomeric purity: 96.3 : 3.7 (R/S)

EXAMPLE 12

(R)-3-Amino-5-methoxy-2H-chroman L-(+)-tartrate.

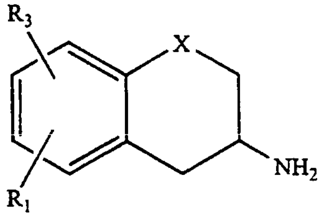
The amine obtained in Ex. 11 (11 g, 61.4 mmol, 1.0 eq.), L-(+)-tartaric acid (9.2 g, 61.4 mmol, 1.0 eq.) and H_2O (275 ml) were charged to a 500 ml three necked round bottomed flask fitted with a mechanical stirrer. The mixture was then heated to a clear solution (~90°C) and then slowly cooled to about 9°C. Seed crystals were added at 60°C. Crystals of the title compound were formed and removed by filtration.

Yield:	Theoretical:	21.3 g
	Found:	17.5 g "(82%)"

Enantiomeric purity: 99.9 : 0.1 (R/S)

CLAIMS

1. A process for the preparation of one of the enantiomers of an amine of the formula (I):

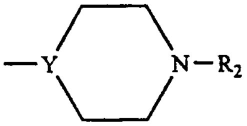


(I)

wherein

X is O or CH_2;

R_1 is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, halogen, OH, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6 alkyl, or



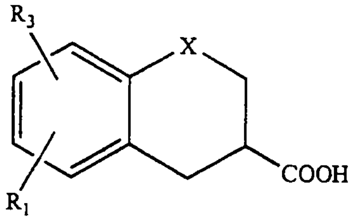
where Y is N or CH; and

R_2 is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl or benzyl; and

R_3 is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, halogen, OH, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6 alkyl, OCF_3, $OCHF_2$, OCH_2F, CN, NO_2, CF_3, SO_3CH_3, SO_3CF_3, NR_4R_5 or $SO_2NR_4R_5$, where R_4 is H, C_1-C_6-alkyl or C_3-C_6-cycloalkyl and R_5 is H, C_1-C_6-alkyl or C_3-C_6-cycloalkyl;

in the form of the free base or a salt or hydrate thereof, which salt or hydrate is preferably pharmaceutically acceptable, which comprises the following steps:

a) subjecting a racemic mixture of a carboxylic acid of the formula (II):



(II)

or a base addition salt or solvate thereof, wherein X, R_1 and R_3 are each as defined in connection with formula (I), to a resolution operation so as to obtain the desired enantiomer and the other enantiomer of said carboxylic acid of formula (II);

b) separating said desired enantiomer from said other enantiomer;

c) subjecting said other enantiomer from step b) to a racemization operation so as to convert the same into a racemate of said carboxylic acid of formula (II);

d) optionally isolating said racemate obtained in step c) in a purified state;

e) recycling and subjecting the racemate as obtained in step c), or alternatively in step d) to a resolution operation as defined in step a) and separating the desired enantiomer thereof as defined in step b);

f) optionally repeating the operations defined in steps c)-e) one or more times;

g) subjecting said desired enantiomer of the carboxylic acid (I) as separated in step b) to a Curtius rearrangement to convert the same into said desired enantiomer of the amine of formula (I);

h) optionally subjecting said desired enantiomer of the amine of formula (I) as obtained in step g) to a resolution operation, the desired enantiomer thereby obtained being recovered; and

i) optionally making base, salt and/or hydrate conversions and/or R_1 and/or R_3 conversions, as appropriate, at any stage(s) of the process.

2. A process according to claim 1, wherein said resolution in step a) is performed by means of an optically active base, preferably an optically active amine, such as an arylalkylamine.

3. A process according to claim 2, wherein said arylalkylamine is phenylethylamine, preferably (R)-(+)- or (S)-(-)-1-phenylethylamine.

4. A process according to any one of claim 2 and 3, wherein said resolution is performed such that the desired isomer salt is crystallized for separation in said crystallized form in step b).

5. A process according to any one of the preceding claims, wherein said racemization in step c) is performed by treating said other enantiomer with an acid anhydride, preferably an organic acid anhydride, and a base, preferably a conjugate base of said acid anhydride or a tertiary amine, said treatment preferably being performed in an organic solvent.

6. A process according to claim 5, wherein said acid anhydride base is acetic anhydride/sodium acetate or acetic anhydride/triethylamine.

7. A process according to any one of claims 5 and 6, wherein said organic solvent is a polar or semipolar solvent, which is preferably selected from isopropyl acetate, tetrahydrofuran, ethyl acetate, dioxane and toluene.

8. A process according to any one of claims 5-8, wherein said racemization is performed at the reflux temperature of the solvent used.

9. A process according to any one of claims 5-8, wherein the amount of acid anhydride/base is in the range of 5-50 mole-% of that of said other enantiomer, prefe-

rably 5-20 mole-% and especially around 10 mole-%.

10. A process according to any one of the preceding claims, wherein said isolation of the racemate obtained in step c) is caused by a crystallization operation so as to obtain the same in said purified state.

11. A process according to any one of the preceding claims, wherein, in a batchwise process, said recycling in step e) is made to a resolution operation batch subsequent to that resolution operation batch from which said racemate originates, preferably the next batch.

12. A process according to claim 11, wherein said recycled racemate is combined with a new feed of racemic mixture of carboxylic acid of the formula (II) such that the total amount of racemic mixture fed to said subsequent step a) is essentially the same as the amount of racemic mixture fed to original step a).

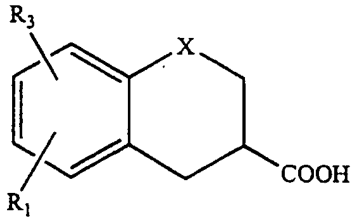
13. A process according to any one of the preceding claims, wherein said resolution in step h) is performed by means of an optically active acid.

14. A process according to any one of the preceding claims, wherein X is O and R_1 is in 5-position and R_3 is in 8-position.

15. A process according to any one of the preceding claims, wherein X is O, R_1 is C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen or OH, and R_3 is H, C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, OH, OCF_3, $OCHF_2$ or OCH_2F.

16. A process according to claim 15, wherein X is O, R_1 is methoxy and R_3 is H.

17. A process for the preparation of one of the enantiomers of a carboxylic acid of formula (II)

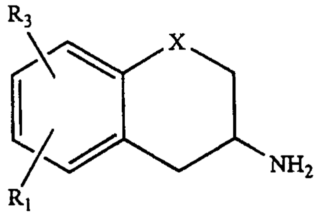


(II)

or a salt of hydrate thereof, wherein X, R_1 and R_3 are each as defined in claim 1, which comprises subjecting a racemic mixture of said acid (II) to a resolution operation so as to obtain the R-enantiomer and the S-enantiomer thereof and separating the desired enantiomer from the other enantiomer, and then performing steps c) and e) and optionally d), f) and i) as defined in claim 1 to recover a further crop of the desired enantiomer.

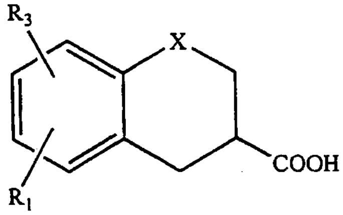
18. A process according to claim 17, which is performed as defined in any one of claims 2-12 and 14-16.

19. A process for the preparation of one of the enantiomers of an amine of formula (I):



(I)

or a salt or solvate thereof, wherein X, R_1 and R_3 are each as defined in claim 1, which comprises subjecting the corresponding enantiomer of a carboxylic acid of formula (II):



(II)

wherein X, R_1 and R_3 are each as defined in connection with formula (I), or a salt or solvate thereof, to a Curtius rearrangement so as to convert the same into the corresponding enantiomer of said amine of formula (I), and then optionally performing steps h) and i) as defined in claim 1.

20. A process according to claim 19, which is performed as defined in any one of claims 13-16.

21. A process according to any one of the preceding claims, wherein said desired enantiomer is the (R)-enantiomer.

22. A process according to any one of the preceding claims, wherein said desired enantiomer is the (S)-enantiomer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00767

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 311/58, C07B 53/00, C07B 55/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Bioorganic & Medical Chemistry Letters, Volume 3, No 10, 1993, M. Langlois et al, "Synthesis of new derivatives of 8-OH-DPAT: influence of substitution on the aromatic ring on the pharmacological profile" page 2035 - page 2038. --	1-16
A	US 5332834 A (APURBA BHATTACHARYA ET AL), 26 July 1994 (26.07.94) --	1-16
A	US 4946997 A (ROBERT D. LARSEN ET AL), 7 August 1990 (07.08.90) -- --------	1-16

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 9 Sept 1999	Date of mailing of the international search report 09 -09- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/ELs Telephone No. +46 8 782 25 00

The subjects, defined by the problems and their means of solution, as listed below are so different from each other that no technical relationship can be appreciated to be present so as to form a single general inventive concept.

1) a process according to claims 1-16

2) a process according to claims 17-18

3) a process according to claims 19-22

The special technical feature of invention 1 is a process for the preparation of one of the enantiomers of an amine (I) by a Curtius rearrangement of the corresponding acid. The process further involves a racemization/resolution operation for the preparation of this acid.

The special technical feature of invention 2 is a process for the preparation of one of the enantiomers of a carboxylic acid (II) from a racemate of this acid by a racemization/resolution operation.

The special technical feature of invention 1 is a process for the preparation of one of the enantiomers of an amine (I) by a Curtius rearrangement of the corresponding acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00767

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see next page

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-16

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.

PCT/SE 99/00767

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5332834 A	26/07/94	AU 5730294 A	22/06/94
		EP 0672029 A	20/09/95
		JP 8503949 T	30/04/96
		US 5380867 A	10/01/95
		US 5399707 A	21/03/95
		WO 9412451 A	09/06/94
US 4946997 A	07/08/90	CA 2018295 A	07/12/90
		EP 0402104 A	12/12/90
		JP 3095127 A	19/04/91

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